Amendments to the Specification

Please replace the title on page 1 with the following title:

Methods ~~and Apparatus~~ for Mass Fingerprinting of Biomolecules

Please replace the paragraph beginning on page 5, at line 27, and ending on page 6, line 20, with the following rewritten paragraph:

In another embodiment, the invention features a method to determine which mass signals from a sample's mass spectrum should be analyzed by tandem mass spectrometry [[MS-MS]] (MS-MS) to confirm or reject determinations of biomolecules and/or biomolecule fragments as likely present in or absent from the sample. In this embodiment, a mass spectrum of the resulting biomolecule fragments is obtained that produces a first spectrum of mass signals which primarily correspond to the biomolecule fragments that make up the biomolecules present in the sample. The signal masses are compared to biomolecule fragment masses in a biomolecule fragment signal list that contains the biomolecule fragments known or predicted to be generated by the digestion and/or fragmentation of a given biomolecule. When a signal mass matches a biomolecule fragment mass, any biomolecule associated with that biomolecule fragment in the list is considered a potential source biomolecule for the corresponding mass signal. A biomolecule score is then assigned to the potential source biomolecule(s). The biomolecule fragment scores and/or biomolecule scores are then used to determine whether a mass signal in the first mass spectrum is subjected to further mass analysis. In one embodiment, only mass signals corresponding to a potential source biomolecule with a high likelihood of being present, as indicated by the biomolecule score, are subjected to MS-MS analysis to confirm or reject the identification and the likelihood of the presence or absence of the biomolecule in the sample. In another embodiment, mass signals that correspond only to a potential source biomolecule with a very low likelihood of being present, or which correspond to no biomolecule in the list, are subject to MS-MS analysis. In another embodiment, mass signal(s) that correspond to two or more potential source biomolecules with comparable biomolecule scores are subjected to MS-MS analysis to confirm or reject the source biomolecule(s) of the mass signals.

Please replace the paragraph beginning on page 19, at line 21, and ending on page 20, line 14, with the following rewritten paragraph. Amendment to equation (1) is being made to delete the character [[N]].

In one embodiment, the biomolecule fragment score is directly proportional to the biomolecule fragment detection parameter and the corresponding matched mass signal intensity and inversely proportional to the relative difference between the signal mass and matched biomolecule fragment mass, as illustrated in equation 1:

$$S[[N]]pp \propto \frac{(I_{ms}) \times (C_{dp})}{((|m_{ms} - m_{pp}| / m_{ms}) + ppm_{min})} \quad (1)$$

where S_{pp} is the biomolecule fragment score, I_{ms} is the intensity of the mass signal in the mass spectrum, C_{dp} is the biomolecule fragment detection parameter, m_{ms} is the corresponding signal mass, m_{pp} is the mass of the matched biomolecule fragment, and ppm_{min} is the minimum ppm error to be considered. The relative mass difference is preferably expressed in ppm. In this embodiment, the term ppm_{min} provides a lower limit for the denominator of equation 1 to prevent division of the numerator by zero. Preferably, the value of ppm_{min} is set to the mass accuracy of the mass spectrometer, because a mass difference less than the limit of accuracy of the mass spectrometer is statistically unreliable. However, it should be understood by one of ordinary skill in the art that whenever the value of a function, such as the biomolecule fragment score or the biomolecule score, is inversely proportional to one of its variables, such as the difference between the signal mass and matched biomolecule fragment mass, a lower limit should be set for this variable by some method to prevent division by zero. In another embodiment, the biomolecule fragment score is directly proportional to the biomolecule fragment detection parameter and the corresponding matched mass signal intensity and inversely proportional to the absolute difference between the signal mass and matched biomolecule fragment mass.

Please replace the paragraph beginning on page 39, at line 13, and ending on page 40, line 5, with the following rewritten paragraph:

In one embodiment, the minimum biomolecule score which indicates a reliable determination that a biomolecule is likely present is determined by offsetting the entire mass scale of the mass spectrum. In this embodiment, the entire mass scale is shifted by a significant number of mass units, such as 3 amu. As a result, with a mass tolerance value of, for example 100 ppm or less, selected in general step 2000, no subsequent mass signal-biomolecule fragment matches should be statistically significant. Accordingly, where the biomolecule score increases with presence likelihood, the maximum biomolecule score obtained by such offsetting represents the biomolecule score below which biomolecules cannot reliably be said to be likely present in the sample. In another embodiment, the biomolecule score calculated in the offset procedure excludes the highest biomolecule fragment score, or scores, from the calculation of the biomolecule score ("YES" to test 4120). This exclusion of the highest biomolecule fragment score, or scores, from the biomolecule score greatly reduces the possibility that a single fortuitous match to a mass signal with high intensity and/or with an associated biomolecule fragment with a high biomolecule fragment detection parameter will dominate the biomolecule score; and as a result, erroneously indicate the likely presence of certain biomolecules which are in fact absent from the sample. In another embodiment, a series of mass scale offsets are performed and the average biomolecule score obtained in the series of offsets is considered the minimum reliable biomolecule score. To further enhance the dependability of the minimum reliable biomolecule score, the biomolecule scores are also preferably weighted by the relative biomolecule fragment match count ("YES" to test 4600), in addition to excluding the highest biomolecule fragment score, or scores, from the biomolecule score determination.

Please replace the paragraph beginning on page 43, at line 8, and ending on page 43, line 21, with the following rewritten paragraph:

In another embodiment, to determine whether the identification of a potential source biomolecule is likely present in a sample is correct, is to consider more than one biomolecule score, weighted biomolecule score, or biomolecule score weighting parameter. Correctly identified biomolecules typically have the highest biomolecule score,

as well as one of the highest weighted biomolecule scores and/or biomolecule score weighting parameters. For example, correctly identified biomolecules typically have one of the highest relative biomolecule intensity values, as well as one of the highest biomolecule fragment counts, and as well as one of the lowest intensity-weighted biomolecule mass errors. Because of this, potential source biomolecules with high biomolecule scores are less confidently identified if they have relative biomolecule intensity values below 20%, or which account for <5% of the intensity that cannot be attributed to higher ranking potential source biomolecules, or have a substantially higher intensity weighted biomolecule mass errors than higher ranking potential source biomolecules.

Please replace the paragraph beginning on page 51, at line 15, and ending on page 51, line 25, with the following rewritten paragraph:

Column 3 shows that the average contribution for fully digested Arg containing peptides is about 55 to 72% of the observed matched signal intensity. Regardless of whether stringency was increased by increasing the required number of matching peptides, by requiring a lower intensity weighted biomolecule mass error, or by requiring a higher percent of matched signal intensity, the percentage of intensity attributable to completely digested Arg containing peptides increased slightly, indicating that the more confident the identification, the more likely the intensity would be accounted for by Arg containing peptides. Column 4 shows that the average contribution for fully digested Lys containing peptides is about 6 to 10% of the observed matched signal intensity. Comparison of columns 3 and 4 shows that the ratio of Arg containing peptide intensity to Lys containing peptide intensity can vary from about 12 to 1 to approximately 5 to 1. As a result, in one embodiment, where the biomolecule fragment detection parameter increases with increasing probability of detection, fully digested Arg containing peptides are assigned a base biomolecule fragment detection parameter of ten (value A in FIG. 4B) whereas fully digested Lys containing peptides are assigned a base value of one (value B in FIG. 4B). The number of fully digested peptides containing arginine detected divided by the number of possible arginine-containing peptides was also calculated, and compared to the fraction of fully digested peptides containing lysine but not arginine.[[.]] It was observed that the percentage of fully digested Arg containing peptides detected varied

from about 67% to about 100% depending on the protein, with an average of roughly 82%. Similarly, it has been observed that the fraction of fully digested Lys containing peptides observed can vary from about 20% to about 62%, with an average of roughly 42%. Accordingly, the ratio of Arg containing peptide fraction observed to Lys containing peptide fraction observed can vary from about 5 to 1 to approximately 3 to 2. In one embodiment, the base value of the biomolecule fragment detection parameter takes into consideration both the relative intensity and relative fraction observed of the biomolecule fragments produced by the fragmentation process used, e.g. Arg and Lys containing peptides when a trypsin digest is used. As a result, in one embodiment, where the biomolecule fragment detection parameter increases with increasing probability of detection, the ratios of the base values of fully digested Arg-containing peptides (value A in FIG. 4B) to the value for fully digested Lys containing peptides (value B in FIG. 4B) is in the range from about 10:1 to 3:2. In one embodiment, the ratio of value A to B is about 10:1. In another embodiment, the ratio of value A to B is about 8:3. However, it should be realized that the exact numerical value of the base biomolecule fragment detection parameter is not crucial to the present invention, and also has little impact on the results. It is to be understood that the base numerical value need only roughly reflect the relative intensity and/or relative fraction observed between fully digested Arg containing and Lys containing peptides.

Please replace the title on page 69 with the following title:

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